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Disease-a-Month

Salmonellosis

HORACE M. GEZON

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HORACE M. GEZON

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THE PROBLEM for the clinician in managing Salmonella infections is ordinarily threefold: diagnosis, treatment and determination of the source of infection. In the presence of an outbreak which is either within a family or community-wide, the diagnosis is relatively easy. In sporadic cases, the diagnosis may be obscure and usually is established late in the disease. When a physician diagnoses one patient as having a Salmonella infection, the probability is great that with close scrutiny, particularly of close associates in the family or within a particular institutional group, others with various degrees of involvement will be found. In the early part of this century, it was the accepted belief that the etiologic diagnosis could be established by clinical manifestations in man. Salmonellas of human origin were thought to produce only enteric fever while those of animal origin produced only mild gastroenteritis. Hormaeche and his co-workers (27) refuted this belief by observing that Salmonellas of animal origin could produce essentially the same clinical diseases in man as those of human origin. This observation applied primarily to Salmonella

disease in children where many different strains were known to produce a quite similar picture. The clinical separation of the Salmonelloses into Salmonella (enteric) fever, Salmonella septicemia and Salmonella gastroenteritis was proposed by Bornstein in 1943 (3). Subsequently, a fourth category, the Salmonella carrier state, was added. While this classification is somewhat artificial, it is useful, inasmuch as it divides the diseases by the clinical syndromes seen rather than by the causative agents. It recognizes that a given species of organism can produce a variety of clinical diseases which are quite dissimilar. It also facilitates the clinical grading of disease by severity, duration and prognosis. For example, the course of illness will be much shorter and the mortality lower with an acute gastroenteritis than with a septicemia of Salmonella origin. Bornstein's categories do not include inapparent infections with these organisms. These are evident only in retrospect when, after a search for the source of a recognized case, a similar type of Salmonella is found by examination of the stools of the patient's associates. In questioning these stool-positive people, it is common to obtain histories of atypical illness or, even more frequently, of no illness.

In general, the specific therapeutic agents, which include chloramphenicol, the tetracyclines, polymyxin B and hymycin, are of limited value in most Salmonella infections. The notable exception is typhoid fever, in which the response to chloramphenicol therapy may be dramatic clinical improvement and a greatly decreased mortality. Even here, however, the frequency of complications such as hemorrhage, intestinal perforations and relapses is not particularly altered by therapy. These comments should not be interpreted as indicating that there are no therapeutic measures which should be applied to the acutely ill patient with a nontyphoid Salmonella infection, but that the principal efforts should be directed toward the correction of dehydration, electrolyte shift and shock which may accompany the disease.

Today, the source of human Salmonella infection in the United States and western Europe is largely of animal origin rather than human. In the United States, major epidemics of the enteric fevers, which were usually water-borne and in some instances milk- or food-borne, now are a rarity. That this can still occur,

however, is attested by the 1955 milk-borne epidemic of *S. paratyphi B* fever in Lancaster, Pa., where 279 infections were reported (61). In England, the reported incidence of Salmonella infections of animal origin has been rising steadily over the past decade (22). In other parts of the world, for example the Middle East, Korea and India, Salmonellas of human origin, including *S. typhosa* and *S. paratyphi A, B* and *C,* continue to play a major role in disease causation.

EPIDEMIOLOGY

Characteristics of the Organism

The general bacteriologic characteristics of Salmonella will not be described here. Certain salient features, however, need to be emphasized. The organism is widespread throughout the animal kingdom. While there are little data on its distribution in wild animals, it seems reasonable to believe that almost all animal groups are involved in this problem. Those of greatest epidemiologic importance for man are poultry and certain mammals, of which the pig is by far the most important (18). Other common domestic animals such as the cat, dog, cow and sheep also are frequent carriers of these organisms and, in fact, may have clinical disease from such infections.

The number of Salmonella species and subspecies recognized is in excess of 400. Nearly half of these have been associated with human disease. Certain types have remained of major importance. For example, *S. typhimurium* continues to be the species isolated most frequently in most countries. The prevalence and distribution of other types have been altered by man's manipulation of his environment. Since 1940, there has been a marked change in the distribution of organisms isolated in England and certain new types have been introduced, some presumably through the importation of dried egg powder or other egg products from other countries (46). From a clinical standpoint, the following new types, *S. anatum, S. bredeney, S. heidelberg, S. reading* and *S. st. paul,* have become of increasing importance and are included in the 10 types most frequently isolated in the year 1957 (22).

When the frequency with which selected Salmonella types are isolated from human sources is given by geographic areas (see table), marked variation within rank order of frequency is observed. Certain types such as *S. typhimurium, S. newport, S. para-*

FREQUENCY OF ISOLATION OF SELECTED SALMONELLA TYPES FROM HUMAN SOURCES BY RANK ORDER AND BY GEOGRAPHIC AREAS

SALMONELLA	1937–47 U.S. (11)	1940–55 MASS. (36)	1950 HAWAII (33)	1947–52 CANADA (7)	1957 ENGLAND (22)	1948–51 NEW ZEALAND (28)
typhimurium	1	1	2	1	1	1
newport	2	3		4	4	
paratyphi B	3	5		2		3
oranienburg	4	4	5	5		
montevideo	5	2	1			
anatum	6	10†	3		6	
choleraesuis	7	12				
derby	8	13	4			
panama	9	11				
muenchen	10	8				
give	11					
bareilly	12	6				
newington	13	10†				
typhosa*	14			3		
san diego	15	14				
heidelberg					2	
enteritidis					3	4
thompson					5	
bovis morbificans					7	2

*The rank order of frequency of *S. typhosa* is difficult to estimate as the reference laboratories do not ordinarily receive cultures for identification.

†*S. anatum* and *S. newington* were combined in this study.

typhi B, S. oranienburg and probably *S. typhosa* tend to be more frequently isolated throughout North America and Hawaii than elsewhere. The comparative data from England and New Zealand show that, while *S. typhimurium* again is the type most frequently isolated, the other Salmonellas frequently isolated in the United States are less common. Frequency data for *S. typhosa* are quite

confusing. Those reference laboratories which have reported large numbers of Salmonella identifications ordinarily do not receive cultures of *S. typhosa,* since the average hospital or public health laboratory is able to make a definitive diagnosis of this particular organism.

It is interesting to speculate on the origin of the many new types which have been recognized in the past 20 years. It is possible, of course, that with refinements in technics of isolation and identification and increased interest in the problem, we are merely recognizing and describing the total number of Salmonellas always extant. It is perhaps just as reasonable to believe that new types are arising by transformation of old types (6), by recombination (32) or through the process of transduction (81).

Mode of Spread

The mode of spread of Salmonellas of human origin theoretically should be easy to demonstrate but in actual practice is seldom accomplished. Most frequently, the convalescent or chronic carrier spreads the organism through fecal contamination of some food substance or water source. Human "error," ignorance or a poor economy makes spread possible. This may be in allowing some food substance to be contaminated by human hands and then incubated long enough to produce the necessary infective dosage of the organism. Error can result in improper pasteurization of fecally contaminated milk or improper treatment of a sewage-contaminated water supply, while ignorance or a poor economy may result in no attempt at treatment. Failure to identify carriers and to eliminate them from food handling may lead to similar results.

The mode of spread of the Salmonellas of animal origin to man is not nearly as well understood. We can only speculate on the various ways in which these organisms are disseminated. A food substance may be contaminated at any time in its preparation. An infectious dose may result either from gross contamination or from minor contamination with subsequent incubation. Human infection takes place when this food is eaten without adequate cooking.

Contamination can take place in the abattoir, in the plant of the meat or poultry processor, in the retail meat market or in the kitchen of the housewife. Alternatively, the food substance may be from a diseased animal brought for "emergency slaughter" or from animals infected just before slaughter. The crowding together of chickens or turkeys, while being raised and when marketed, increases the likelihood of spread within a flock. Similarly, the crowding of animals while being transported to market and in holding pens before slaughter permits a single excreter to infect a large number of other animals. This method of spread in pigs has been documented in the studies of Galton *et al.* (18). Only a few animals may be excreting the organisms or have it in the blood, mesenteric lymph nodes or gut contents, but by the time the knife has opened the gut and then been used on successive animals, many carcasses may be contaminated by the same organism. In turn, the butcher's or the housewife's hands, utensils or cutting blocks can transfer the organism from this source to some other food.

The most important single source of the Salmonellas is poultry. Turkeys, because of their size and in particular after being stuffed, are difficult to sterilize adequately. In the baking process, the organism may merely be incubated so that an infectious dose results. Duck and chicken carcasses also have been found to harbor large numbers of organisms and here the housewife's hands may serve to disseminate the pathogen to other food media. Shell eggs and egg products, such as dried egg powders and dried or frozen egg whites, have frequently yielded a large variety of Salmonellas in many parts of the world (45). This has been true particularly for products shipped from China or from South American countries.

Another mechanism of animal-to-human spread can be through feeding household pets raw meat or dehydrated dog foods, both of which have been demonstrated to be contaminated frequently with Salmonellas. The dog or cat after infection excretes the organism, and humans handling these animals can in turn transfer the agent to food substances or even directly to the mouth. Galton *et al.* (17) have shown that domestic pets are frequently fecal carriers of these enteric pathogens.

It is obvious, therefore, that there are many mechanisms of transfer of animal Salmonellas to man and that not all of them are readily accessible to control.

Dosage

The importance of the difference in dosage necessary to produce disease by the several Salmonella species, as well as strains within a given species, needs to be appreciated. McCullough and Eisele (42, 43) in a series of studies using human volunteers have demonstrated these differences. They tested strains of 6 Salmonella species. All had been obtained from dried egg powders and were of the types most commonly found in egg powders by other investigators. The variation in the minimum infectious dose for two strains of *S. anatum* was 587,000 and 44,500,000 organisms. With *S. pullorum,* dosages in the billions were required to produce even a transient illness in volunteers. With *S. meleagridis,* strain 2, when 5.5×10^6 organisms were fed, none of the 6 subjects became ill; with a dosage of 1×10^7 organisms, 1 of 6 became ill; with 2×10^7 organisms, 2 of 6 and with 4.1×10^7 organisms 5 of 6. Interestingly, the shortest incubation period (10–12 hours) occurred in the volunteer who became ill after receiving the lowest dosage and the longest incubation period (72 hours) in the one receiving the highest dosage. These studies emphasize the strain and species differences as well as the importance of the dosage size.

Gradient of Clinical Involvement

A problem of considerable interest to both the clinician and the epidemiologist concerns the spectrum of response manifested by persons who are simultaneously exposed to a given organism. It is well known that after exposure some people show no infection or infection without disease, whereas others develop clinical illness and die. The gradient between these two extremes deserves attention. Human response to Salmonella exposure is determined by the specific immunity and nonspecific resistance of the host, as well as by the dosage and the characteristics of the particular organism.

The differences in response to infection are exemplified in Figure 1, which is an approximation of the percentages falling within the various clinical categories for 4 Salmonella species. For example, if the agent is *S. anatum,* the likelihood of a typhoid-like or septicemic illness is small, as this organism characteristi-

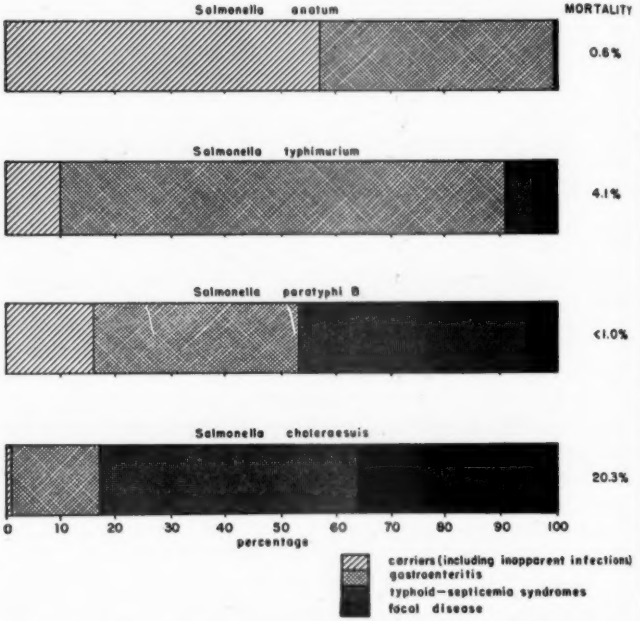

FIG. 1.—Gradient of clinical involvement, with selected Salmonella types. Sounce of data: references (11) and (60).

cally produces either inapparent infection or symptoms predominantly of the gastrointestinal tract. However, at times *S. anatum* can produce the picture of enteric fever and it has been isolated from the blood (11). Therefore, in most instances either this organism has poor invasive ability or man has a nonspecific resist-

ance to it. When enteric fever and septicemia occur, it may be due either to unusual properties of a particular strain or to decreased resistance of the host. With an organism such as *S. typhimurium,* a far higher percentage of infected persons will show symptoms of a typical gastroenteritis of fairly brief duration. Here again there are variations in response. A certain number of persons will develop a typical enteric fever picture and perhaps as many as 4 or 5% will die. Relatively few will have inapparent infection, although the frequency can only be estimated. *S. paratyphi B,* like *S. typhimurium,* produces a simple gastroenteritis frequently, but, in contrast to *S. typhimurium,* it often produces enteric fever, although it rarely causes death.

In contrast to the other 3 organisms, human infection with *S. choleraesuis* commonly results in septicemia with or without localization (59) and rarely inapparent infection or just gastroenteritis. It is attractive to postulate that this Salmonella has unique properties that give it great invasiveness in man as well as in its natural host, the pig.

The recent Lancaster epidemic due to milk-borne *S. paratyphi B* exemplifies the problem of determining an actual gradient. The estimate of magnitude of the outbreak, based on a house-to-house culture and questionnaire survey during the epidemic, indicated that there were actually 1,505 rather than the reported 279 persons infected. Of this number, 480 had a clinical illness resembling enteric fever or gastroenteritis, 603 had an atypical illness and 422 inapparent infections (61). It is obvious from these data that a gradient based on reports accompanying cultures, such as was used to construct Figure 1, can be quite inaccurate.

Invasion by any of the Salmonellas may fail to take place when the host has acquired immunity through prior exposure to an antigenically related organism, when the host has a high level of nonspecific resistance, e.g., properdin system, or when the organism has altered pathogenicity. In a point or single source epidemic caused by a given strain of any of these organisms, the whole gradient of involvement is ordinarily present. It is probable that there are variants or mutants with differing pathogenic capabilities in the bacterial population making up the total inoculum for the epidemic. Whether or not a person received organisms of low or high pathogenicity would be a chance phenomenon and

could explain variation in the subsequent course. While this theoretically could occur, there is no experimental proof that this actually takes place. It is much more likely that the critical factors that determine the nature and severity of disease are dosage of the agent and the host's defenses.

CLINICAL MANIFESTATIONS

Certain clinical entities, mentioned previously, categorize the Salmonelloses. They include gastroenteritis, enteric fever and septicemia with and without focal disease.

Salmonella Gastroenteritis

Salmonella gastroenteritis in the sporadic case is not easily distinguishable clinically from other acute diarrheal diseases, for example, shigellosis or even staphylococcal food poisoning. In the presence of an epidemic, there are identifying features that aid in diagnosis. These include a history of ingestion of certain foods, incubation period, presence or absence of fever, type of onset and duration of symptoms. A typical story for an average young adult with Salmonella gastroenteritis would be as follows: Approximately 12 hours before the onset of this illness he attended a church picnic, at which time he ate turkey salad sandwiches. These had been prepared by the food committee the day before and reportedly had been refrigerated overnight. The patient felt well until night, when he awakened with severe nausea. He vomited profusely and then felt better, although there was some abdominal "uneasiness." Soon diffuse abdominal pain alternating with severe cramps appeared. This was followed by diarrhea, loose, foul-smelling stools at first, then greenish and watery and, finally, bloody in character. Fever was present for the first 2 days.

A story such as this is commonly obtained but variation in the symptomatology may be expected in both the experimental and the natural disease. In experimental infection (42) with a given strain of Salmonella, the disease was reported to vary from an afebrile illness with 3–4 watery stools to one with chills, vomiting,

abdominal cramps and 40 watery stools over a 2-day period. While the usual story in natural infection indicates nausea and vomiting as the herald symptoms, it is not uncommon to find fever, abdominal pain or diarrhea separately, or in combination, with or without nausea and vomiting. The degree of severity of the signs and symptoms also varies. The diarrhea may range in severity from a single loose stool up to 20–30 liquid projectile stools per day. In the latter situation, these may be grossly bloody. At times, the abdominal pain may be localized and the intensity so severe that acute appendicitis or pleurodynia is suggested. The fever also may range from none, in approximately half of the patients, to levels approaching that seen in enteric fever or septicemia.

The clinical picture in small infants and young children may be quite different from that described above. Hormaeche, *et al.* (27) have emphasized that the diarrhea may be so mild that it is unnoticed; dysenteriform in character with mucoid, bloody stools simulating acute shigellosis; or choleriform in type with the rapid development of severe dehydration, prostration and shock resulting from fluid and electrolyte loss.

The gastroenteric syndrome caused by Salmonella infection is not always clearly distinguished from other clinical varieties of this disease. An illness may begin with primarily gastrointestinal symptoms and then develop characteristics of either the enteric fever or septicemic variety of the disease. Bacteremia is probably common in all febrile patients. Whether the bacteremia results in focal lesions in the liver and spleen or results in meningitis, pulmonary abscesses or osteomyelitis depends somewhat on the patient's age, associated diseases and defense mechanisms. The small infant and the debilitated adult are likely candidates for the complications of septicemia. There also are certain predisposing conditions which appear to result in localization of the bacteria, viz., sickle cell anemia (26), carcinoma and hematomas (21).

The etiology of gastroenteritis is not indicated by the symptomatology. Many species of Salmonella can produce this clinical picture. Gastroenteritis caused by *S. typhosa,* while rare, is clinically indistinguishable from gastroenteritis due to *S. anatum, S. typhimurium* or *S. choleraesuis.* However, certain Salmonellas seem to

have a predilection for causing the gastroenteritis syndrome, as is exemplified in data from two recent reports:

Salmonella	1939–55 Saphra and Winter (60)		1940–55 MacCready, *et al.* (36)	
	Total No. Isolations	% from Gastro-enteritis Patients	Total No. Isolations	% from Gastro-enteritis Patients
typhimurium	2,385	81	868	79
newport	701	77	232	75
muenchen and manhattan	254	77	64	73
enteritidis	240	76	71	82
montevideo	659	71	290	68
anatum and newington	346	68	50	62
oranienburg	641	65	197	63
derby	182	65	37	68
panama	234	55	45	71
bredeny	82	54	23	70

In contrast to this, none of the isolations of *S. paratyphi A*, 2% of *S. typhosa* and 15% of *S. choleraesuis* (11) were from patients with gastroenteritis. *S. typhimurium* occupies a unique position in the causation of gastroenteritis. In most areas of the world it is both the most commonly found organism in epidemics of gastroenteritis and the organism most likely to produce this syndrome (60).

Enteric Fever

The classic picture of enteric fever is that of the patient with typhoid fever. Osler's (52) description based on 1,500 cases occurring at Johns Hopkins Hospital at the end of the past century can hardly be improved on:

"During the first week there is, in some cases (but by no means in all, as has long been taught), a steady rise in the fever, the evening record rising a degree or a degree and a half higher each day, reaching 103° or 104°. The pulse is not rapid when compared with the temperature,

full in volume, but of low tension and often dicrotic; the tongue is coated and white; the abdomen is slightly distended and tender. Unless the fever is high there is no delirium, but the patient complains of headache, and there may be mental confusion at night. The bowels may be constipated or there may be loose movements often due to purgation. Toward the end of the week the spleen becomes enlarged and the rash appears in the form of rose-colored spots, seen first on the skin of the abdomen. Cough and bronchitic symptoms are common at the outset.

"In the second week, in cases of moderate severity, the symptoms become aggravated; the fever remains high and the morning remission is slight. The pulse is rapid and loses its dicrotic character. There is no longer headache, but there are mental torpor and dullness. The face looks heavy; the lips are dry; the tongue, in severe cases, becomes dry also. The abdominal symptoms, if present—diarrhea, tympanites, and tenderness—become aggravated. Death may occur during this week, with pronounced nervous symptoms, or, toward the end of it, from haemorrhage or perforation. In mild cases the temperature declines, and by the fourteenth day may be normal.

"In the third week, in cases of moderate severity, the pulse ranges from 110 to 130; the temperature shows marked morning remissions, and there is a gradual decline in the fever. The loss of flesh is more noticeable, and the weakness pronounced. Diarrhea and meteorism may occur for the first time. Unfavorable symptoms at this stage are the pulmonary complications, increasing feebleness of the heart, and pronounced delirium with muscular tremor. Special dangers are perforation and haemorrhage.

"With the fourth week, in a majority of instances, convalescence begins. The temperature gradually reaches the normal point, the tongue clears, and the desire for food returns. In severe cases, the fourth and even the fifth week may present an aggravated picture of the third; the patient grows weaker, the pulse is more rapid and feeble, the tongue dry, and the abdomen distended. He lies in a condition of profound stupor, with low muttering delirium and subsultus tendinum, and passes the faeces and urine involuntarily. Failure of the circulation and secondary complications are the chief dangers of this period.

"In the fifth and sixth weeks protracted cases may still show irregular fever, and convalescence may not set in until after the fortieth day. In this period we meet with relapses in the milder forms or slight recrudescence of the fever. At this time, too, occur many of the complications and sequelae."

While this description is still an excellent one, certain features no longer are characteristic of the disease. The sustained temperature elevation is rarely encountered. Instead, marked daily fluctuations in temperature of the so-called septic type are usually seen. There is no ready explanation for this change in picture. The dry lips, dry tongue and loss of flesh described by Osler represent dehydration and malnutrition. These should not be seen when the patient is properly treated, even in the absence of specific antibiotic therapy.

The picture in patients with disease caused by organisms other than *S. typhosa* is slightly different and, in general, somewhat less severe. The onset may be quite abrupt and the patient may be able to remember precisely the hour the illness started. The initial symptoms ordinarily are malaise and fever which begin at a fairly low level and gradually increase over the first few days of the illness. Ordinarily, there is no leukopenia; in fact, leukocytosis is common. Splenomegaly and slow pulse rate in relation to the height of the fever are unusual signs. Rose spots may occur with certain Salmonellas, whereas with others they never occur. Abdominal pain is commonly found, and this may be associated with either diarrhea or constipation—more likely the former. Severe diarrhea may be a quite early symptom. Patients with enteric fever have been operated on for acute appendicitis both because of the localization and the severity of the pain (13). Pulmonary symptoms suggesting bronchitis are seen early in the illness, while signs of bronchopneumonia are occasionally present relatively late. These also are less likely to appear than in typhoid fever. The usual course of the disease tends to be considerably shorter and less stormy than that of untreated typhoid fever. The duration of illness rarely exceeds 14 days. Hemorrhage and perforations are rare complications.

Just as with the gastroenteritis syndrome, certain species of Salmonella have a predilection for producing the picture of enteric fever or septicemia. This is illustrated in the following data from northeastern United States by certain Salmonellas selected on the basis of highest frequency:

Salmonella	1939–55 Saphra and Winter (60)		1940–55 MacCready, *et al.* (36)	
	Total Isolations	% from Patients with Typhoidal or Septic Syndromes	Total Isolations	% from Patients with Typhoidal or Septic Syndromes
paratyphi A	40	68	3	0
choleraesuis and paratyphi C	359	48	27	56
paratyphi B	349	41	94	37.2
panama	234	17	45	9
oranienburg	641	8	197	5
san diego and st. paul	133	8	23	13

S. paratyphi A was the one most likely to produce these syndromes when present but the least likely one to be found. *S. choleraesuis* was commonly found and was also likely to produce the syndromes.

Salmonella Septicemia

This disease entity resembles that of enteric fever with the exception that the temperature tends to be more spiking in character and focal manifestations are likely to be seen early in the illness. These manifestations include appendicitis, cholecystitis, localized or generalized peritonitis, salpingitis, bacterial endocarditis, pericarditis, pneumonia and pleurisy, urinary tract infection, acute osteomyelitis, osteoarthritis and abscess formation. Abscesses tend to occur in areas contiguous with the gastrointestinal tract, including periproctal, perineal, subphrenic and appendiceal locations. Brain, skin, lung and splenic abscesses have also been reported.

Focal manifestations can occur in infection with many types of Salmonella. In Saphra and Winter's (60) data there were 572 patients with focal manifestations; of these, 128 were caused by *S. choleraesuis* or *S. paratyphi C,* 117 by *S. typhimurium,* 56 by *S. oranienburg,* 32 by *S. newport,* 26 by *S. montevideo,* 28 by *S. panama* and the balance divided among many other types.

The site of localization varies considerably. For example, certain diseases such as sickle cell anemia, Mediterranean anemia and other anemias with abnormal hemoglobin predispose to Salmonella osteomyelitis. *S. paratyphi B, S. typhimurium* and *S. choleraesuis* are the organisms most often found in osteomyelitis associated with these anemias. These 3 species accounted for 22 of 33 reported cases up to 1957 (26). It is not known why a particular site is selected by the organism, but it seems reasonable to believe that local factors such as thrombosis, infarction and other pathologic changes interfering with defense mechanisms could promote localization. In sickle cell anemia, for example, the unusual incidence of localization of Salmonella infections has been explained (26) by (1) lowered local tissue resistance due to ischemia and necrosis subsequent to capillary thrombosis caused by sickling and (2) lowered total body resistance due to general debility with anemia and the effects of autosplenectomy.

Meningitis is a focal manifestation largely limited to infants. In Henderson's (25) review of the literature up to 1948, there were 147 cases (exclusive of *S. typhosa* patients) that could be identified with reasonable certainty as Salmonella meningitis. In this group the age distribution was as follows:

<1 mo.	1–11 mos.	1–13 yrs.	Adults	Age Unknown
49	51	18	11	18

The disease was frequently epidemic in the very young infant and was usually preceded by diarrhea. In older children and adults, a gastrointestinal disease ordinarily did not precede the meningitis and the cases were sporadic. The case fatality rate in infants under 1 month was 98% and that in older children and adults was 79%. The recoveries were largely limited to patients with *S. paratyphi A* or *B* and *S. panama* infections. It should be noted that the only specific therapeutic agents available during this time period were sulfonamide and streptomycin. This mortality could be interpreted, therefore, as that in the untreated patient with Salmonella meningitis.

In reported cases of Salmonella meningitis, a relatively small number of types was responsible for most of the incidence. This may be seen in the following summary:

Salmonella	1909–1948 Henderson (25)	1943–1953 and Smith (66)	1939–1955 Saphra and Winter (60)
enteritidis	38		7
paratyphi B	23		2
havana	21		1*
panama	18		12
typhimurium	17		9
choleraesuis	8		9
enteritidis var. jena, dublin, etc.	8		
paratyphi A	7		
bredeney	5		11
other types†	16		26
Total	161		77

*Only one representative strain was received from an epidemic of 21 cases of meningitis caused by this organism.

†Exclusive of *S. typhosa*.

PROBLEMS AND CLINICAL FEATURES ASSOCIATED WITH CERTAIN TYPES OF SALMONELLA

S. Typhosa

There are many features of the disease produced by *S. typhosa* which are fairly unique and the most outstanding of these should be examined in some detail.

Intestinal hemorrhage is a frequent occurrence in typhoid fever. The reported incidence ranges from 5.1% in Osler's 389 patients (51) to 21.1% in 360 cases reported in 1948 from New Orleans Charity Hospital (69). This complication, which can occur in patients both with and without antibiotic therapy, usually appears late in the second or in the third week of illness. In Stuart and Pullen's (69) series it was first detected, on the average, on the 15.7th day of the disease, with a range of 7–41 days. Both hemorrhage and the subsequent perforations can be correlated with the pathologic changes in the second and third weeks of the disease. During the first week of illness, the organism is reproducing maximally in the biliary tract and probably the duodenum. The lymphoid tissue of the small intestines is continually "invaded" by the bacilli, which are phagocytized by plasma cells of Peyer's patches, and these in turn, after degeneration, are ingested by

macrophages (20). Mallory (39) considered the large mononuclear phagocytes, which are the characteristic cellular manifestation of this disease, to be of vascular endothelial origin. Others (4) believe they are derived from the reticuloendothelial system. There is general agreement, however, that regardless of the origin or nature of these cells, the basic lesion in *S. typhosa* disease is productive in character and comprised of mononuclear cells which have largely replaced the normal cellular structure of Peyer's patches and of the solitary glands of the jejunum and ileum. The lower 18 inches of the ileum characteristically shows maximal involvement. Hyperplasia and hyperemia result in swelling of the lymphoid masses so that by the end of the first week of the disease these are projecting above the inner surface of the gut. At about this time, necrosis of the epithelium begins, in part due to endotoxins of the organism and in part to small thrombi from accumulation of phagocytes in the walls of small blood vessels (39). During the second week of the illness, the necrotic epithelium sloughs off, leaving shallow ulcers. The submucosa is also frequently involved. Hemorrhage results when the necrosis extends into the vascular plexus of the submucosa. The number and size of the ulcerations bear little relationship to the severity of the illness (19).

Intestinal perforations are produced when the necrotic process extends through the muscularis and the peritoneum of the gut. They have been observed in patients with mild illness as well as in those who had apparently recovered. They occur in about 1–3% of all patients. In Stuart and Pullen's series, proved perforations occurred in 2%. The mean time of appearance was the 19th day of illness with a range from the 12th to 27th day. The usual signs suggesting perforation are severe abdominal distention with meteorism, appearance of sudden sharp pain of increasing severity, lower abdominal tenderness on palpation, abdominal rigidity and leukocytosis. This complication accounts for ¼ to ⅓ of deaths from typhoid fever, and hemorrhage and perforation combined account for 75% of the deaths.

Roseola, the so-called rose spot of typhoid fever, while observed in *S. paratyphi A* and *B* infections, is found typically in *S. typhosa* enteric fever. It is observed with clinical typhoid fever in 80–90% of white adults, a somewhat lower percentage of

white children and about 15–20% of Negroes. The lesions usually appear in crops between the 7th to 10th day of illness. Individual lesions are slightly elevated, 2–4 mm. in size, rose-pink in color and persist for about 48 hours. They blanch on pressure. The distribution ordinarily is limited to the anterior and lateral surfaces of the lower thorax and abdomen and the lesions number less than a dozen at one time. The pathogenesis is thought to be lodgment and clumping of organisms in the lymphatics of the skin papillae. Positive cultures have been obtained from lesions (52).

Leukopenia, with related agranulocytosis, absence of eosinophils and increase in large mononuclear cells are characteristic of typhoid fever. These findings are usually most prominent in the third and fourth weeks of the illness, when the total leukocyte count is likely to be 5,000 or less. The pathogenesis of the hematologic shift appears to be replacement of the normal constituents of the red marrow by the typical typhoid mononuclear cell and lymphocytes (35). A similar leukopenia with associated chills, fever, headache and malaise has been produced in man through the intravenous injection of a purified somatic antigen prepared from *S. typhosa* (12). Comparable bone marrow changes have been produced in rabbits with the same material (48).

Anemia is commonly observed in both complicated and uncomplicated typhoid fever patients. The usual type (52, 69) is probably due to bone marrow alteration and is marked by decreasing hemoglobin and red blood cell levels which reach minimum values in the third week of illness. During convalescence, the anemia gradually disappears. A second type of anemia is caused by gradual or sudden blood loss from bleeding ulcerative lesions of the gut, the pathogenesis of which has been discussed earlier. A third, and much more unusual, type is due to hemolysis. The onset is acute and ordinarily occurs within the first 2 weeks of illness. The diagnostic signs are jaundice, hepatomegaly, splenomegaly (more so than would be expected at this stage of typhoid fever), severe toxemia and, in some instances, hemoglobinuria. In a report of 6 cases (44), one of which had hemoglobinuria, the urine and feces were positive for urobilinogen, red cell counts ranged from 1.8 to 2.8 million per cm., serum bilirubin from 2.2 to 3.6 mg. %, reticulocytes from 8 to

14% and the direct Coombs test was positive in the 4 patients on whom it was performed. The authors of the report concluded that this complication was a symptomatic acquired hemolytic anemia and its pathogenesis was probably not directly due to the effects of *S. typhosa* but rather to the reticuloendothelial hyperplasia produced in the disease process. The response of their patients to ACTH supported this conclusion.

Respiratory tract involvement in typhoid fever has been noted by most investigators, and the degree ranges from coryza to bronchitis to pneumonia and lung abscess. Stuart and Pullen (69) reported cough to be present in 86%, rales in 65% and pneumonia in 11% of their 360 patients. They attributed the rales mainly to hypostatic pulmonary congestion and the pneumonia to secondary bacterial invaders. In only one of their patients was *S. typhosa* cultured from the sputum. Neva (49) observed pulmonary signs in 65% of a group of 80 patients with *S. typhosa* or *S. paratyphi A, B* or *C* enteric fevers. The signs in order of frequency were rales, rhonchi, decreased breath sounds, squeaks, dullness and wheezes. In this study, pneumonia also occurred in 11% of the patients, and again *S. typhosa* was isolated from the sputum of only 1. Neva postulated that the signs and symptoms resulted largely from injury to the bronchial epithelium, presumably from some product of the organism. This could be analogous to the tissue damage induced in rabbits by a purified somatic antigen of *S. typhosa* (48).

Central nervous system manifestations are invariably present in the severely or moderately ill patient with typhoid fever. The earliest symptoms, headache and insomnia, as well as the later ones, delirium, drowsiness, deafness and urinary retention are considered evidence of toxicity presumably from some product of the organism. In small children, signs of meningismus and convulsions are not unusual. The pathogenesis of the CNS manifestations is poorly understood, but presumably the signs and symptoms result from the effects of the endotoxin. Pathologic changes in the brain are rare. The exception to this latter statement is typhoid meningitis where the usual findings of a purulent process are observed.

The *carrier state,* both convalescent and chronic, is a major

problem with *S. typhosa*. The term convalescent carrier usually refers to those who are fecal or urinary excreters of the organism during the first year after the acute illness and chronic carrier refers to those who excrete for a period longer than a year. It has been estimated (71) that 8.6% of typhoid patients become temporary or convalescent fecal carriers, 4.2% convalescent urinary carriers and 3.3% chronic carriers. These percentages have relatively little meaning unless they are further analyzed by age and sex.

When the carriage rates were broken down by age of patients at the time of illness the following distribution was obtained:

Age in Years	% Convalescent Carriers	% Chronic Carriers
0–15	7.5	0.9
16–30	13.4	0.8
>30	14.3	8.0

The sex ratio in the convalescent carrier in this study was 2 females to 1 male, in chronic carriers 4:1 and total cases 1:1. In a classic study of chronic carriers in New York State, Ames and Robbins (1) reported similar findings. From their data, it is clear that the marked difference in the sex ratio was largely limited to ages 30–49. This is shown in the following:

Age in Years at Time of Typhoid	% of Cases Resulting in Chronic Carriers	
	Male	Female
<10	0.6	—
10–19	0.4	0.2
20–29	2.1	2.1
30–39	2.8	6.2
40–49	3.5	16.4
50–59	9.1	11.5
>60	6.2	9.4
Total	2.1	3.8

The duration of convalescent carriage, as was mentioned previously, in the United States is legally considered to be up to 1 year after illness. The duration period of excretion after the acute illness is expressed in weeks in the following (71):

	Total Number Patients	Duration of Excretion in Weeks				
		1	2	3	4	>4
Feces	31	8	9	6	4	4
Urine	15	1	5	5	–	4

It is evident that the period of temporary carriage is limited in most patients. Vogelsang and Bφe (71) found only 1 out of a total of 413 patients who spontaneously stopped excreting the organism more than 3 months after the onset of the disease. They concluded that this was a better time interval than the usual 1 year after illness to delineate the chronic excreter.

The pathogenesis of cholecystitis, cholelithiasis and the chronic carrier state in *S. typhosa* infections is reasonably well known. The organism is ingested with food or water and most of the inoculum is capable of passing through the acid stomach and into the duodenum. The lymphoid tissue of the entire small intestine, but particularly the ileum, is invaded by the bacilli. The mesenteric lymph nodes are the next site of invasion. After multiplication here, the organisms pass through the thoracic duct to the general circulation and finally lodge in numerous sites, including the liver, spleen, bone marrow and, in particular, the gallbladder. Gay (19) reported that bacilli could be recovered from the gallbladders of experimentally infected rabbits within 30 minutes after intravenous infection of *S. typhosa*. In man, inflammatory lesions develop in the wall of the gallbladder, and the organism may be recovered from them. The bacilli apparently multiply both in these lesions and in the bile and in turn are excreted via the bile duct to the gut. In certain people with pre-existing gallbladder disease, there is an increased likelihood that the organism will persist, resulting, subsequently, in cholecystitis and/or cholelithiasis. *S. typhosa* has been isolated from the interiors of bladder stones. Smith (67) has demonstrated submucosal inflammatory lesions made up of large mononuclear cells in gallbladders removed at operation from chronic carriers, and these resemble the typical acute typhoid lesions found in other tissues.

The pathogenesis of the urinary carriers is presumably similar to that of the fecal ones. Again, pre-existing disease, in particular that resulting from schistosomiasis, increases the likelihood of the development of chronic urinary carriage. In the Middle East, this creates an important public health problem.

S. Paratyphi A

Enteric fever produced by this organism resembles in most of its characteristics that from *S. typhosa*. It differs, however, in these respects: (1) less severe illness with shorter course and lower mortality, (2) lower frequency of the classic typhoidal signs, viz., splenomegaly, leukopenia and rose spots, (3) less tendency to relapse and (4) less tendency for chronic carriers to result.

This organism rarely produces the gastroenteritis syndrome, although symptoms referable to the gastrointestinal tract are common in the enteric fever which it produces. Saphra and Winter (60) observed the gastroenteritis syndrome in only 3 of 40 patients with *S. paratyphi A* infections and Edwards *et al.* (11) in none of 29.

Intestinal hemorrhage with or without perforations is more common than is generally recognized. The pathogenesis is similar to that in typhoid fever. Zimmerman *et al.* (80) and Hardy (23) observed a high incidence of ileal ulcerations and perforations in Korean and Chinese POWs. *S. paratyphi A* was cultured in most instances from the lesions at autopsy. Hardy estimated there were approximately 10,000 cases of *S. paratyphi A* infections in the POW camps, with 200 resulting in intestinal perforations.

S. Paratyphi B

Either enteric fever or gastroenteritis may be caused by this organism. There are no characteristics of the enteric fever produced by this agent that distinguish it from that caused by *S. paratyphi A,* with the exception of less frequent intestinal perforation.

The gastroenteritis may be quite mild and be misdiagnosed as a nonspecific diarrhea. Many persons in an epidemic have inapparent infections and their condition is recognized only through their contact with clinical cases. The pathogenesis of this syndrome is poorly understood and the pathologic lesions insignificant. Presumably, the living organism is required to initiate the disease since attempts to produce the disease experimentally with killed organisms or their products have been generally unsuccessful.

Convalescent carriers of *S. paratyphi B* are found frequently but chronic carriers are rare. The differences in convalescent fecal carrier rates by time after the illness as well as between epidemics is illustrated in the following data:

Week after Onset of Illness	% Still Positive	
	Lancaster, 1955 (61)	Mass., 1937–43 (57)
1	100	100
4	62	62
8	26	22
20	1	8
30	0	6
50	0	5

The carrier state persists longer in persons with clinical illness than in those who are infected but remain asymptomatic. In the Lancaster epidemic, none of 36 persons with inapparent infection was positive after the 8th week, whereas 31 of 173 (18%) of those who had had clinical disease were still excreting the organism at this time.

S. Choleraesuis

The unique ability of this organism to produce septicemia with localization in many sites, as well as its ability to kill, distinguishes it from all other Salmonellas. This is well demonstrated in the report on 359 patients by Saphra and Winter (60). *S. choleraesuis* produced the typhoid or septic syndromes without localization in 48% of these patients, the syndromes with focal manifestation in 36%, gastroenteritis in 15% and the carrier state in 1%. Death occurred in 20% of the total. In an earlier analysis of part of the same group of patients, Saphra and Wasserman (59) reported the typhoid or septic syndromes could be further divided into 10% with the typhoid-like illness and 90% with septicemia.

The localization in children, typically, is meningeal, bone or joint. The resulting meningitis, osteomyelitis or pyarthrosis is usually chronic, at times indolent in nature and always difficult to treat. Organisms reinvade the blood stream repeatedly, resulting in exacerbation of the septicemia and localization in other sites. The mortality in both treated and untreated patients is high.

The typical focal lesions of typhoid fever in the spleen and liver are also seen in *S. choleraesuis* infections while the gastrointestinal tract lesions are rare. Endocarditis, cholecystitis, urinary tract infection, respiratory tract infections—in particular pneumonia—salpingitis and abscesses in almost any location are the other characteristic focal manifestations produced by this organism. In all of these conditions the duration of disease is long and frequently it terminates in death.

Characteristically, the organism is found only in the blood or in the focal abscesses and infrequently in the stool (60). This results in few convalescent or chronic carriers.

The association of *S. choleraesuis* (also called *Salmonella suipestifer* in the early literature) with other diseases has been commented on by Harvey (24). It is seen with unusual frequency in postsurgical patients, in patients with cancer, in persons with scurvy or other nutritional deficiencies, in diabetic people and in association with other acute infectious diseases.

THERAPY

Chloramphenicol in Typhoid Fever

The treatment of most Salmonella infections, with the notable exception of typhoid fever, is still largely symptomatic therapy. While there have been enthusiastic reports of the effectiveness of successive new antibiotics against Salmonella, in general these claims have not been substantiated. However, evidence has been steadily accumulating, since the first report (77) in 1948, that chloramphenicol is a most useful therapeutic agent in typhoid fever. It has a prompt effect on the clinical course of the disease and has markedly lowered the case fatality rate. It has not, however, lowered the incidence of certain complications nor has it eliminated relapses or the carrier state.

Therapy with chloramphenicol has varied according to *quantity of drug and duration of treatment.* The original dosage schedule proposed by Woodward *et al.* (77) was 50 mg. of chloramphenicol per kg. body weight as a "priming" dose, followed by 0.25 Gm. every 2 hours until the temperature was normal, and then 0.25 Gm. every 3 hours for 5 days. On this regimen, the duration of

fever averaged 3.5 days after therapy was started, but 2 of the first 10 patients relapsed and 2 developed complications—an intestinal perforation and a massive hemorrhage. In the next group of patients, the same investigators (64) changed the dosage to an initial 3–4 Gm. of chloramphenicol, followed by 1–3 Gm. daily, divided into 2 doses. In 13 patients treated for 8 days or less, there were 7 relapses, while in 31 treated for 9 to 23 days there was none. Intestinal hemorrhages and perforations continued to be a problem and their incidence was not decreased by therapy. The authors' explanation for this observation was that lesions in the intestine had already developed before institution of therapy and that tissue changes proceeded independently of the presence of *S. typhosa*. Chloramphenicol was not effective in the treatment of chronic typhoid carriers (76).

In the past 10 years, numerous other investigators have used chloramphenicol at various dosage levels and with various schedules. In general, with the exception of absence of relapses after prolonged therapy, their findings have confirmed most of the early reports. El Ramli (10) treated 398 cases of typhoid and paratyphoid fever with 12.5 mg./kg. of chloramphenicol every 12 hours. Of these cases, 81% were diagnosed as having been caused by *S. typhosa*. Nearly half of the patients were under 5 years of age. The average duration of fever after therapy was 3.7 days. The patients were divided into 3 groups by treatment schedules. In the first, totaling 289 patients, chloramphenicol was given as long as the fever persisted or up to 3 days after the temperature reached normal. There were 26.3% relapses in this group. In the next 58 patients, treatment was stopped when the temperature became normal and then resumed again in the second week of convalescence when relapses would be expected. There were 13.8% relapses in this group. In the third group of 51 patients, therapy was continued for 12 days after the temperature became normal; the relapse rate was 3.9%.

The *time in the course of the illness when chloramphenicol is started* seems to play a role both in frequency of relapses and mortality. Marmion (40) obtained relapse rates of 36.0, 25.5 and 19.7%, respectively, when therapy was started in the first, second and third weeks of the disease and a total case fatality rate of 1% in his series of 330 patients. As opposed to this, El Ramli (9) obtained relapse rates of 16.7, 25.5 and 31.4% respectively, when

treatment was started in the corresponding time periods and case fatality rates of 0, 4.5, 9.0 and 15.0% in these periods plus any time greater than 3 weeks. While both of these studies were conducted in Egypt at about the same time, the former was in military personnel and the latter in natives. Nutritional levels, age distribution and presence of associated disease undoubtedly contributed to these contradictory results.

Chloramphenicol therapy seems to be *associated with a higher relapse rate*. Woodward and Wisseman (78) have summarized the reported data on relapse rate in patients treated with chloramphenicol. The average rate was 18.3%. When this is compared with results obtained in the preantibiotic era, it is higher than that reported in any large series of cases. Representative examples are Osler (52), 11.4%, McCrea (41), 8.8% and Stuart and Pullen (69), 12.5%. The cause for this increase, presumably, is interference with immune mechanisms by the antibiotic. Shortly after the drug is given, the organism can no longer be isolated from the blood (78), and the antigenic stimulus therefore may be diminished. The best evidence supporting this concept is obtained from the studies in which patients starting therapy early in the course of disease had higher relapse rates than those starting treatment late. Another effect of chloramphenicol postulated by Watson (72) is that it increases the rate of phagocytosis, thereby causing more organisms to be intracellular. These intracellular bacilli are partially protected from the action of the antibiotic as well as from humoral antibodies and presumably may be available to start the disease when the drug is stopped. The observations of Magoffin and Spink (38), who showed that intracellular Brucella are protected from the action of antibiotics, and Rous and Jones (56), who demonstrated that intracellular *S. typhosa* are protected from circulating antibodies support this postulate.

Chloramphenicol has also been used in *combination with vaccine* in an attempt to reduce the relapse rate. Marmion (40) observed a total relapse rate of 28.3% in typhoid patients treated with chloramphenicol. However, when this report is analyzed according to treatment schedule, the rates were 18.2% in patients receiving continuous chloramphenicol therapy for about 14 days, 17.6% with this plus phenolized typhoid vaccine daily for the first 10 days, 42.3% with chloramphenicol in two courses interrupted by a 7-day interval and 4.8% with this interrupted schedule

plus vaccine. The difference in relapse rates in those receiving and not receiving typhoid vaccine was striking, particularly when the vaccine was combined with intermittent chloramphenicol therapy. The number of patients (21) on that regimen was so small that these results can be interpreted only as being suggestive. Rapellini and Di Nola (54) obtained comparable striking differences (8 vs. 29%) in 24 patients treated with chloramphenicol alone and 28 with this plus vaccine. The rationale for the concurrent use of typhoid vaccine was stimulation of antibody production which may not have occurred by natural means due to suppression of *S. typhosa* by chloramphenicol. It was thought that by artificial immunization, antibodies would be produced which would destroy both intra- and extracellular bacilli.

Chloramphenicol therapy has produced *no reduction in the incidence of intestinal hemorrhage or perforation* in typhoid patients and there is suggestive evidence that it may have increased it. The incidence of perforations in studies before antibiotic therapy was available range from 1% in Osler's series (52), 2% in Stuart and Pullen's (69) to 3.1% in McCrea's (41). In chloramphenicol-treated patients comparable figures are 0.7% in Marmion's series (40), 3.5% in El Ramli's (10) and 5.1% in the Malayan studies (78). The incidence figures for intestinal hemorrhage are also comparable in the treated and untreated patients, although the variations between studies is much wider.

The incidence of convalescent but not chronic carriers of S. typhosa has been reduced by chloramphenicol therapy of acute typhoid fever. This is well demonstrated in a study of 614 untreated and 799 treated patients in Louisiana and Mississippi (50). The results of treatment of chronic carriers with this antibiotic reported by many investigators have been almost uniformly negative.

Chloramphenicol *can cause complications* besides being of only limited effectiveness in the treatment of certain aspects of *S. typhosa* infection. These complications include:

1. Direct toxicity manifested by vomiting, fever and albuminuria.
2. Allergic manifestations, including urticaria, skin rashes, agranulocytosis and delayed fever.
3. Secondary effects from rapid release of bacterial endotoxin, producing a toxic crisis.

4. Alteration of microbial balance, with moniliasis as an example.

The third complication listed deserves elaboration. This is an infrequent but most serious problem seen only in the very severely ill typhoid fever patient (40). Galpine (16) has postulated that the crisis is due to liberation of endotoxin from the killed organisms. The principal signs and symptoms in an instance of fatal toxic crisis reported by Stephens (68) were rapid fall in temperature, feeble pulse, tachycardia and restlessness. This reaction resembles the Jarisch-Herxheimer reaction seen in syphilis. To prevent fatal crisis, Friedman (15) recommended treating the "hypertoxic" patient initially with supportive therapy and then cautiously giving small doses of chloramphenicol after the most acute phase has passed. The use of cortisone and, in patients with shock, norepinephrine would be rational.

Cortisone and ACTH in Typhoid Fever

The use of cortisone alone or in conjunction with chloramphenicol has been investigated in the treatment of typhoid fever (65, 74, 75). The results have been gratifying, particularly in acutely toxic patients. Fever, headache, mental dullness and other manifestations of toxemia were reported to abate in 15 hours with intramuscular and 6 hours with oral cortisone. This may be contrasted with amelioration of symptoms in 3–4 days with chloramphenicol alone. The initial dosage used was from 200 to 300 mg. followed by 100–200 mg. daily for 3 days. Compound A (11-dehydrocorticosterone) has been demonstrated to be effective against the "shocking action" of typhoid endotoxin in the adrenalectomized rat (34). Presumably, the effect of cortisone in man is analogous. Since it has neither bactericidal nor bacteriostatic effect, it should ordinarily be used jointly with chloramphenicol. Bacterial complications associated with its use have been reported in typhoid patients (58). Cortisone therapy is not recommended routinely for all typhoid fever patients, but may be lifesaving in critically ill persons.

Hormones also have a place in the therapy of the rare patient with acute hemolytic anemia associated with typhoid fever.

McFadzean and Choa (44), using ACTH, and Braude (5), using cortisone, demonstrated prompt reversal of the hemolytic process.

Therapy in Other Salmonelloses

There have been a number of reports of success in treating the other Salmonelloses with oxytetracycline, chlortetracycline and chloramphenicol (14, 30, 55, 62, 79). Undoubtedly, some patients, particularly those with meningitis and enteric fever, have responded to these therapeutic agents, but most of the reports of success cannot be evaluated, as they represent uncontrolled studies. It is well known that patients with the various forms of Salmonella disease recover without therapy. Even with *S. choleraesuis* septicemia, the case fatality rate is probably not over 20%, and with the other Salmonellas the rate in untreated patients is ordinarily less than 5%. Macdonald *et al.* (37) studied 51 children with proved Salmonella enteritis: 48 caused by *S. typhimurium*, 2 by *Salmonella adelaide* and 1 by *Salmonella derby;* 25 received chloramphenicol at a level of 125 mg./kg. daily for 10 days and 26 received no specific therapy. The selection of patients for the two regimens was made without regard to the severity of the illness on the basis of odd and even numbers taken from a table of random numbers. Patients in both groups received fluid and electrolyte replacement as needed and their diet, which included skim milk, was identical. The children were considered to be moderately ill and were having from 8 to 20 stools per day. Relatively few, however, showed severe clinical dehydration requiring the use of intravenous fluids. The following data show convincingly that in each age category there was no statistically significant difference between the duration of illness in the treated and control groups.

Mean Duration in Days from Start of Treatment to Clinical Cure (37)

Age No./group	<3 Mo. 8	3-6 Mo. 13	6-12 Mo. 22	12-18 Mo. 6	18-24 Mo. 2
Chloramphenicol	21.8(6–41)*	12.2(9–16)	14.8(7–32)	10.3(7–12)	Nil
Controls	18.5(11–30)	15.9(9–33)	13.8(3–30)	7.3(0–15)	8.5(8–9)

*Range in parentheses.

The children in each age group were divided approximately evenly between the treatment and control groups. The authors concluded that chloramphenicol played no particular role in influencing the rate of clinical recovery nor did it alter the bacteriologic state of these persons. The organism disappeared at approximately the same time in both groups.

The value of antibiotics in the treatment of carriers of the many Salmonellas also is unsettled. LaCore and Conlin (31) reported chloramphenicol to be effective in 23 of 25 mental hospital patients who were carriers of one type (16) or multiple types (9) of Salmonella. *S. montevideo, S. oranienburg* and *S. tennessee* were the predominant types found. It is difficult to evaluate this study, as the duration of carriage before or after therapy was not stated. The disappearance of the organisms would likely have occurred without any therapy in most instances. The 8% failure is not too different from the expected number of permanent carriers from these types. Temporary convalescent carriage of these types is common and permanent carriage rare (57).

The value of any of the antibiotics in the treatment of Salmonella infections (excluding *S. typhosa*) remains a moot point. The evidence is certainly less than convincing that they play a determining role in the course of the disease. This is illustrated in a patient at the University of Pittsburgh Medical Center. The patient was a 67-year-old church custodian who developed acute diarrhea and vomiting the day after eating a ham supper at his church. The diarrhea was severe, with watery stools every half hour. He was treated with penicillin, sulfadiazine and nonspecific antidiarrheal therapy by a local physician but failed to improve over the next 6 days. Vomiting and frequent nonbloody liquid stools persisted. He had intermittent fever and a single chill. He gave a history of having had typhoid fever at 8 years of age.

The principal findings on admission to the hospital were: temperature 97.4 F, weakness, lethargy, dehydration, white lesions on the buccal mucosa (*Monilia albicans* was demonstrated) and normal findings on examination of the chest and abdomen. Laboratory data showed hemoglobin 18.8 Gm., hematocrit 56%, WBC 9,200, urine normal, BUN 120 mg. %, sodium 127 mEq./L., potassium 3.4 mEq./L., chloride 94 mEq./L. and CO_2 20 mM/L. The initial stool cultures were negative for bacterial pathogens.

Admission diagnoses of gastroenteritis, severe dehydration and thrush were made.

The patient received intravenous fluids and electrolytes, including potassium chloride, for his dehydration and mycostatin ointment topically for his thrush. On the second hospital day, he became febrile and physical signs and chest x-ray suggested bronchopneumonia and pulmonary congestion. The patient was digitalized and penicillin and chloramphenicol were started. The antibiotics were changed first to kanamycin and then to streptomycin and chloramphenicol when *Escherichia coli* and coagulase + *Staphylococcus aureus* were cultured from his sputum. Increasing signs of oliguria, an increase in BUN to 250 mg. %, hyponatremia and negative urinalysis suggested acute renal tubular necrosis secondary to the severe dehydration. *S. enteritidis* was cultured from the stool on the second and the blood on the fifth hospital day. Despite intensive therapy with antibiotics, oxygen, digitalization and fluid and electrolyte replacement, the patient ran a steadily downhill course. He died on the tenth day of hospitalization.

At autopsy, the principal findings were: (1) acute enterocolitis, (2) massive bilateral bronchopneumonia and left lung abscess, (3) stomatitis and esophagitis from which *Monilia albicans* was cultured and (4) acute tubular necrosis. *S. enteritidis* was cultured from the small bowel, right and left lungs, lung abscess and a bronchial lymph node.

Several lessons in the management of Salmonellosis are emphasized by this case: (1) the dehydration and electrolyte disturbance demand prompt and vigorous correction, (2) antibiotics may be of little help and, in fact, Monilia infections may result from antibiotic usage and (3) one Salmonella disease, in this instance typhoid fever, may be followed by an infection with a closely related organism (both have the IX, XII somatic antigens). This case also emphasizes that Salmonella enteritis is not necessarily a benign disease. The adverse outcome of this case, especially the failure of antibiotics to effect a cure should not be interpreted to mean that the physician is without therapeutic measures. In many severe Salmonella infections, patients survive when meticulous attention is given to the level of hydration, electrolyte balance, symptoms of shock, presence of associated diseases and state of nutrition of the patient.

Selection of Antibiotic

The use of antibiotic sensitivity testing of Salmonella organisms obtained from clinical material should be mentioned. With the Salmonellas in general, this is a useless procedure. If one were to use the antibiotic sensitivity for selecting a drug to treat typhoid fever patients, chloramphenicol would rarely be chosen, since the organisms are ordinarily relatively resistant to this drug as compared, for instance, with streptomycin. This applies equally well to other Salmonellas where there is poor correlation between the results of therapy and the results of antibiotic sensitivity testing. Weiner and Liebler (73) have observed this clinically as have Seligmann and Wasserman (63) in experimental *S. typhimurium* infections in mice. The latter found that oral or subcutaneous chloramphenicol given for 8 days merely prolonged survival without affecting the mortality. They attributed these results to the bacteriostatic property of the drug.

LABORATORY DIAGNOSIS OF SALMONELLA INFECTIONS

The diagnosis of all forms of Salmonella disease rests ultimately on culturing the organism from the patient's blood, stool, urine, spinal fluid or other source. The optimal time to find the agent in these locations depends on the particular species of Salmonella and the particular variety of disease. For example, in *S. typhimurium* gastroenteritis the bacilli will be found in the stool within the first few days of illness and then gradually disappear over the next several weeks. Blood and urine cultures may be positive at this time, but this is the exception; ordinarily, they remain negative. In enteric fever caused by any of several Salmonellas, blood cultures are usually positive early in the course of the disease, whereas the feces and urine become bacteriologically positive somewhat later. In septicemia, the blood is also positive early while the feces and urine may never be positive. If the septicemia is accompanied by focal manifestations, the organism can be found in exudation or aspiration from the focal lesion, e.g., joint fluid, spinal fluid, pus, sputum, etc., at any time during the acute phase of the illness.

Typhoid fever is an excellent example to illustrate the importance of relating the time the specimen is obtained to the stage of

the illness. Coleman and Buxton (8) reported positive blood cultures in 89% of their patients in the first and 73% in the second week of illness. More recently, Batty Shaw and MacKay (2) obtained results of 80% and 90%, respectively, in the first and second weeks of illness in untreated patients. By the fifth or sixth week of the disease, relatively few untreated patients will have positive blood cultures. In contrast to this, stool and/or urine cultures are positive in approximately 50% of typhoid patients in the first week but nearly 80% by the second week. There is a steady decline, during convalescence, in the number of patients excreting the organism, but as was discussed previously, some convalescent carriers may in turn become chronic carriers and excrete the bacilli for life. Similarly, there may be an elevated anti-O or H agglutinin titer in the first week of typhoid fever in about 20% of the patients, whereas from the second to fifth weeks nearly 100% will demonstrate this. Figure 2 represents as estimation of frequency of positive results by week of illness. The data used to construct the graphs are from old reported studies. With better culture media now available and with the determination of anti-O rather than anti-H agglutinins, the exact percentages might be quite different, but the trend would likely be the same.

Stool Culture

Rectal swabs, fresh stool or stool preserved in neutral glycerin are suitable for culture studies. The combination of a highly selective medium such as Shigella-Salmonella (SS) Agar (Difco), Brilliant Green Agar (BBL) or Bismuth Sulfite Agar (Difco) plus a less inhibitory medium such as MacConkey's Agar (Difco) is preferred in most clinical laboratories for initial plating of the specimen. The use of an enrichment broth, either tetrathionate containing brilliant green and iodine or Selenite F, will increase the likelihood of finding a carrier but adds little in diagnosing acute infection. The details of identifying nonlactose fermenting colonies on these media are beyond the scope of this article. It will suffice to mention that a competent bacteriologist should be able to alert the physician in 16–24 hours that suspicious colonies are present and, in some instances, make a presumptive diagnosis

at that time by direct agglutination with polyvalent somatic serum of organisms from selected colonies. It will likely require 2 or 3 days to confirm this presumptive identification. The final indentification of the species is ordinarily made by a Salmonella reference laboratory.

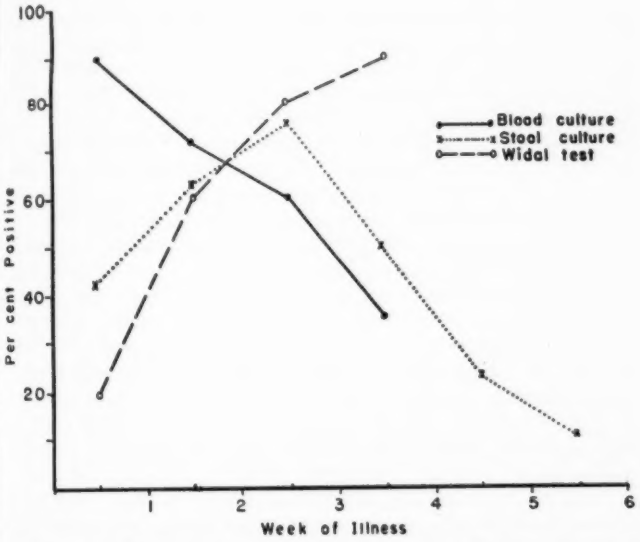

FIG. 2.—Laboratory data in typhoid fever, by week of illness. Source of data: references (8) and (53).

Infection from more than one Salmonella type may occur simultaneously in a single patient. This has been reported in several studies (29,61,73) with as many as 5 types of Salmonella cultured from a single stool specimen. Juenker (29) found multiple types in 13 of 75 people who were examined because they were known Salmonella carriers. As many as 489 colonies per specimen were studied in obtaining these results. This, of course, is not practical for the average diagnostic laboratory, but it does

emphasize that at least several colonies should be examined from each specimen.

Blood Culture

The Salmonellas are not fastidious organisms and grow well in a variety of broths and in the presence of oxygen. Ordinary meat infusion broth or one of the dehydrated preparations such as Tryptose Phosphate Broth (Difco), Tryptose Broth (Difco) or Trypticase Soy Broth (BBL) give satisfactory results. It is advisable to have a ratio of 1 part blood to 10 to 20 parts of broth to decrease the inhibitory effect of antibodies in the patient's serum. The use of a blood clot rather than whole blood will also increase the probability of obtaining a positive culture. The length of incubation required to obtain growth will vary widely from patient to patient. Batty Shaw and MacKay (2) reported the average period of incubation of the culture required to obtain positivity was 4–5 days, and, in 17% of 76 patients, 9–11 days of incubation was needed. It is clear from these data that the clinician should not expect a definitive answer from the laboratory on morning rounds the day after the patient's admission. In addition, it should be emphasized that the mere presence of growth (turbidity) in the broth culture does not mean a positive culture. The Gram stain of smears prepared from this will be helpful, but the identification must be made in a manner similar to that for stool pathogens.

Multiple blood cultures should be taken on patients suspected of having Salmonella septicemia or enteric fever. It is ordinarily taught that the blood culture should be taken at the height of fever. Batty Shaw and MacKay (2) have demonstrated that the probability of success is greater when this is done but that positive cultures may be obtained from enteric fever patients even at the time of subnormal temperature.

Urine, Spinal Fluid and Pus

These are cultured preferably on both solid and liquid media. The methods used for isolation and identification from feces and blood apply equally well to these materials. The length of incuba-

tion will likely be considered shorter than that required for blood cultures as the number of organs is ordinarily much greater than in blood.

Agglutination Test

The Widal test has been used as a diagnostic test for typhoid fever for more than 60 years. The test originally was done with a formalinized suspension of organisms and thus measured anti-H agglutinins. At present, clinical laboratories ordinarily use both O and H antigens for *S. typhosa,* and H antigens for *S. paratyphi A, B* and *C*. Antigens for the other Salmonella groups are also available commercially. The original tube test has been replaced or supplemented in many laboratories by a rapid slide agglutination technic. The results with the two tests are not identical but, practically, both methods are adequate.

The value of this test is greatest when the antigens used are titrated against standard antisera and when paired sera, acute and convalescent, are tested at the same time. These conditions are rarely met. It is more likely that a single serum sample is available for test. The clinician usually interprets an anti-O titer of 1:50 or 1:80 or an anti-H titer of 1:100 or 1:150 for *S. typhosa* diagnostic. There are many pitfalls in accepting such an interpretation. If the patient has received *S. typhosa, S. paratyphi A* and *B* vaccine previously, the anti-H agglutinins will likely be elevated to a titer of 1:100 or higher and even the anti-O agglutinin titer may be elevated if vaccine had been administered within the preceding 6 months. The sharing of antigens, both O and H, by related Salmonellas may lead to misinterpretation of elevated agglutinin titers. For example, *S. typhosa* and *S. enteritidis* share the same O antigens, IX, XII, whereas *S. paratyphi B* and *S. typhimurium* not only have the same O antigens, (I) IV, (V), XII but also the same phase 2, H antigens, 1, 2. A diagnosis based on an elevated agglutinin titer can be only an approximation which needs confirmation through culture studies. A final problem in the interpretation of an elevated agglutinin titer is the anamnestic antibody response to a related or unrelated antigen. Such a response is common and may suggest that the patient has a Salmonella infection when, in fact, he has a disease caused by a completely unrelated infectious agent.

PREVENTION OF SALMONELLA INFECTIONS

Prevention may be effected through altering the environment or through increasing the resistance of the host. There has been more measurable success with the former, viz., control of carriers and water, milk and food sanitation, than with the latter, viz., vaccination.

The spread of Salmonellas of human origin may be controlled by regulating the activities of acute cases of disease and carriers to prevent these people from handling food and by proper control of water and milk supplies. The major success in Salmonella control has been through the provision of potable water supplies and safe, pasteurized milk sources. There are numerous problems encountered, however, when regulation of carriers is attempted. As was mentioned earlier, there are many carriers of Salmonella who admit to no clinical illness related to these organisms. Obviously, these carriers will be recognized only, if by chance, they are cultured and the organism identified. It could be argued that commercial food handlers who are carriers would be located if there were strictly enforced laws requiring periodic stool culture examination.

In general, industry resists having its employees cultured and the employees resist being cultured. Another problem is that of being able to examine food handlers frequently enough to insure their remaining free of pathogens. Carriers are usually intermittent shedders so that serial cultures would be necessary to accomplish this. Even if a food handler were found to be negative after a series of examinations, there is no assurance that he would remain that way. A new infection could follow immediately. An alternate approach is through education of food handlers to teach them proper personal hygiene and to teach them to use utensils instead of their hands in preparing food. Again, theoretically, this should be possible, but in practice relatively little is accomplished.

The problem of preventing the transmission of animal Salmonellas to man is, if anything, a more difficult one to solve. The sanitation of dairy products and provision of safe water supplies have solved part of this problem. The veterinarian's inspection of animals at time of slaughter will find only the most

grossly diseased animals, but not the equally dangerous, recently infected ones. There is also no practical way of keeping the carcass of the animal from becoming contaminated by spread from other animals during the processing and dispensing of the meat. Another problem is that of shell eggs and, in particular, of frozen and dried egg products. The usual method for preparing dried egg products generates insufficient heat to sterilize them. Most large batches of dried whole eggs, egg yolks or egg whites, therefore, contain viable Salmonella organisms. There are methods available to sterilize these products, but these have not been adopted, as they change the characteristics of the food substance.

Perhaps the best approach to prevention of spread of these animal Salmonellas is through education of the housewife as to the dangers inherent in the handling of any raw meat or poultry in her kitchen, the necessity for washing her hands before handling other foods which are not subsequently cooked and the need for particular care in roasting stuffed products such as turkeys. It is obvious from this brief discussion of food sanitation that we are far from a solution to these problems at present.

The other approach to prevention is through increasing host resistance. Vaccines containing *S. typhosa, S. paratyphi A* and *B* (TAB) have been available for nearly 60 years. The efficacy of this vaccine has never been adequately determined and there are some today who feel it is of little or no value. Others are convinced that there is sufficient evidence to say that the vaccine at least reduces the severity of illness and probably prevents some infections. There is no question that in the presence of heavy exposure the vaccine will not prevent infection. The experience of the British army in the Suez (47) and the United States army in the Pacific (70) firmly attest to this. Controlled field studies, presently being carried out in various parts of the world, should help settle the question of the real value of the current vaccines.

There are many who feel that one or more representative strains of group C Salmonella should be included in the polyvalent vaccine. This is based on the increasing incidence of diseases caused by members of this group. This would certainly seem to be a logical development and one worthy of trial.

The American Public Health Association presently recommends inoculation of international travelers with triple typhoid vaccine

(TAB) for travel in parts of the world where epidemics of typhoid and paratyphoid fever are to be expected. Until evidence is presented to the contrary, the use of vaccine should be recommended for people such as these at particular risk. The present recommended dosage is three weekly subcutaneous injections of 0.5 ml. of TAB vaccine followed by a booster dose of 0.5 ml. subcutaneously or 0.1 ml. intradermally at yearly intervals while at particular risk. The efficacy of the intradermal method has not been fully evaluated but antibody studies suggest that it approximates the potency of the subcutaneous booster dose. In addition, systemic reactions are appreciably less frequent and intense with the antigenic mass contained in the intradermal dose.

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